WHAT IS CLAIMED IS:

1. A method for obtaining a cell-specific binding molecule useful for increasing uptake or specificity of a genetic vaccine to a target cell, the method comprising:

creating a library of recombinant polynucleotides that by recombining a nucleic acid that encodes a polypeptide that comprises a nucleic acid binding domain and a nucleic acid that encodes a polypeptide that comprises a cell-specific binding domain; and

screening the library to identify a recombinant polynucleotide that encodes a binding molecule that can bind to a nucleic acid and to a cell-specific receptor.

2. A method for obtaining a cell-specific binding moiety useful for increasing uptake or specificity of a genetic vaccine to a target cell, the method comprising:

(1) recombining at least first and second forms of a nucleic acid which comprises a polynucleotide that encodes a nucleic acid binding domain and at least first and second forms of a nucleic acid which comprises a cell-specific ligand that specifically binds to a protein on the surface of a cell of interest, wherein the first and second forms differ from each other in two or more nucleotides, to produce a library of recombinant binding moiety-encoding nucleic acids;

(2) transfecting into a population of host cells a library of vectors, each of which comprises: a) a binding site specific for the nucleic acid binding domain and 2) a member of the library of recombinant binding moiety-encoding nucleic acids, wherein the recombinant binding moiety is expressed and binds to the binding site to form a vector-binding moiety complex;

(3) lysing the host cells under conditions that do not disrupt binding of the vector-binding moiety complex;

(4) contacting the vector-binding moiety complex with a target cell of interest; and

(5) identifying target cells that contain a vector and isolating the optimized recombinant cell-specific binding moiety nucleic acids from these target cells.

3. The method of claim 2, wherein the method further comprises:

(6) recombining at least one optimized recombinant binding moiety-encoding nucleic acid with a further form of the polynucleotide that encodes a nucleic acid binding domain and/or a further form of the polynucleotide that encodes a cell-specific ligand, which are the same or different from the first and second forms, to produce a further library of recombinant binding moiety-encoding nucleic acids;

(7) transfecting into a population of host cells a library of vectors that comprise: a) a binding site specific for the nucleic acid binding domain and 2) the recombinant binding moiety-encoding nucleic acids, wherein the recombinant binding moiety is expressed and binds to the binding site to form a vector-binding moiety complex;

(8) lysing the host cells under conditions that do not disrupt binding of the vector-binding moiety complex;

(9) contacting the vector-binding moiety complex with a target cell of interest and identifying target cells that contain the vector; and

(10) isolating the optimized recombinant binding moiety nucleic acids from the target cells which contain the vector; and

(11) repeating (6) through (10), as necessary, to obtain a further optimized cell-specific binding moiety useful for increasing uptake or specificity of a genetic vaccine vector to a target cell.

4. The method of claim 2, wherein the method further comprises identifying cell-specific binding moieties that result in the highest efficiency in transfecting the target cells.

5. The method of claim 2, wherein the nucleic acid binding domain is a DNA binding domain derived from a protein selected from the group consisting of a transcriptional regulator, a polypeptide involved in DNA replication or recombination, a repressor, a histone, a protamine, an *E. coli* CAP protein, myc, a protein having a leucine zipper, a protein having a DNA binding basic domain, a protein having a POU domain, a protein having a zinc finger, and a protein having a Cys_3His box.

6. The method of claim 2, wherein the nucleic acid binding domain is an RNA binding domain derived from a protein selected from the group consisting of HIV *tat* and HIV *rev*.

7. The method of claim 2, wherein the target cell of interest is selected from the group consisting of muscle cells, monocytes, dendritic cells, B cells, Langerhans cells, keratinocytes, and M-cells.

8. The method of claim 7, wherein the cell of interest is a professional antigen presenting cell.

9. The method of claim 8, wherein the antigen presenting cell is a dendritic cell, a monocyte/macrophage, a B cell, or a Langerhans cell.

10. The method of claim 8, wherein the cell-specific ligand comprises a polypeptide selected from the group consisting of CD2, CD28, CTLA-4, CD40 ligand, fibrinogen, ICAM-1, Fc portion of immunoglobulin G, and a bacterial enterotoxin, or a subunit thereof.

11. The method of claim 2, wherein the target cell of interest is a human cell.

12. The method of claim 2, wherein the target cells that contain the vector are identified by selecting for expression of a selectable marker contained in the vector.

13. The method of claim 2, wherein the optimized recombinant binding moiety-encoding nucleic acid comprises a genetic vaccine vector.

14. A cell-specific recombinant binding moiety produced by expressing in a host cell an optimized recombinant binding moiety-encoding nucleic acid obtained by the method of claim 2.

15. A genetic vaccine that comprises a cell-specific recombinant binding moiety of claim 14.

16. A genetic vaccine that comprises an optimized recombinant binding moiety-encoding nucleic acid obtained by the method of claim 2.

17. A genetic vaccine that comprises:

a) an optimized recombinant binding moiety that comprises a nucleic acid binding domain and a cell-specific ligand, and

b) a polynucleotide sequence that comprises a binding site, wherein the nucleic acid binding domain is capable of specifically binding to the binding site.

18. A method for obtaining an optimized cell-specific binding moiety useful for increasing uptake, efficacy, or specificity of a genetic vaccine for a target cell, the method comprising:

(1) recombining at least first and second forms of a nucleic acid that comprises a polynucleotide which encodes a non-toxic receptor binding moiety of an enterotoxin, wherein the first and second forms differ from each other in two or more nucleotides, to produce a library of recombinant nucleic acids;

(2) transfecting vectors that contain the library of nucleic acids into a population of host cells, wherein the nucleic acids are expressed to form recombinant cell-specific binding moiety polypeptides;

(3) contacting the recombinant cell-specific binding moiety polypeptides with a cell surface receptor of a target cell; and

(4) determining which recombinant cell-specific binding moiety polypeptides exhibit enhanced ability to bind to the target cell.

19. The method of claim 18, wherein the cell surface receptor is present on the surface of a target cell.

20. The method of claim 18, wherein the cell surface receptor is G_{M1}.

21. The method of claim 18, wherein the host cell is a *V. cholerae* cell which is incapable of expressing CT-A.

22. A method for enhancing uptake of a genetic vaccine vector by a target cell, the method comprising coating the genetic vaccine vector with an optimized recombinant cell-specific binding moiety produced by the method of claim 18.

23. The method of claim 18, wherein the recombinant cell-specific binding moieties are expressed as a fusion protein on the surface of a replicable genetic package.

24. A method of obtaining a genetic vaccine component that confers upon a vector an enhanced ability to enter an antigen-presenting cell, the method comprising:

creating a library of recombinant nucleic acids by subjecting to recombination at least two forms of a polynucleotide;

contacting a library of vectors, each of which comprises a member of the library of recombinant nucleic acids, with a population of antigen-presenting or antigen-processing cells; and

determining the percentage of cells in the population that contain the vector.

25. The method of claim 24, wherein the antigen-presenting or antigen-processing cells are selected from the group consisting of B cells, monocytes/macrophages, dendritic cells, Langerhans cells, keratinocytes, and muscle cells.

26. The method of claim 25, wherein the cells are B cells which are obtained from a B cell line.

27. The method of claim 24, wherein the screening is conducted *in vivo* and the cells are monkey cells or mouse cells.

28. The method of claim 24, wherein the method further comprises:

culturing the cells for a predetermined time after contacting the cells with the library of vectors;

washing the cells after the contacting step to remove vectors that did not enter an antigen-presenting cell; and

isolating the vectors from the cells that contain a vector.

29. The method of claim 24, wherein the cells that contain a vector are identified by:

transfecting individual library members or pools of library members into separate cultures of antigen-presenting cells;

co-culturing the cultures of antigen-presenting cells with T lymphocytes obtained from the same individual as the antigen-presenting cells; and

identifying cultures in which a T lymphocyte response is induced.

30. The method of claim 29, wherein the T lymphocyte response is selected from the group consisting of increased T lymphocyte proliferation, increased T lymphocyte-mediated cytolytic activity against a target cell, and increased cytokine production.

31. The method of claim 24, wherein the vector is a replicable genetic package and the recombinant nucleic acids are expressed as a fusion protein which is displayed on the surface of the replicable genetic package.

32. The method of claim 31, wherein the replicable genetic package is a bacteriophage.

33. A method of obtaining a genetic vaccine component that confers upon a vector an enhanced ability to enter cell or tissue when administered to a mammal by a desired administration protocol, the method comprising:

creating a library of recombinant nucleic acids by subjecting to recombination at least two forms of a polynucleotide;

administering to a mammal a library of vectors, each of which comprises a member of the library of recombinant nucleic acids, into a mammal;

obtaining target cells or tissues from the mammal;
identifying target cells or tissues that contain a vector, and
recovering vectors from the identified target cells or tissues.

34. The method of claim 33, wherein the target cells are lymphatic cells.

35. The method of claim 33, wherein the administering is by oral ingestion, inhalation, injection, or topical application to skin or mucous membrane.

36. The method of claim 33, wherein the vector is a replicable genetic package and the recombinant nucleic acids are expressed as a fusion protein which is displayed on the surface of the replicable genetic package.

37. A method for evolving a vaccine delivery vehicle to obtain an optimized delivery vehicle having enhanced ability to enter a selected mammalian tissue upon administration to a mammal, the method comprising:

(1) recombining members of a pool of polynucleotides to produce a library of recombinant polynucleotides;

(2) administering to a test animal a library of replicable genetic packages, each of which comprises a member of the library of recombinant polynucleotides operably linked to a polynucleotide that encodes a display polypeptide, wherein the recombinant polynucleotide and the display polypeptide are expressed as a fusion protein which is which is displayed on the surface of the replicable genetic package; and

(3) recovering replicable genetic packages that are present in the selected tissue of the test animal at a suitable time after administration, wherein recovered replicable genetic packages have enhanced ability to enter the selected mammalian tissue upon administration to the mammal.

38. The method of claim 37, wherein the method further comprises:

(4) recombining a nucleic acid that comprises at least one recombinant polynucleotide obtained from a replicable genetic package recovered from the selected tissue

with a further pool of polynucleotides to produce a further library of recombinant polynucleotides;

(5) administering to a test animal a library of replicable genetic packages, each of which comprises a member of the further library of recombinant polynucleotides operably linked to a polynucleotide that encodes a display polypeptide, wherein the recombinant polynucleotide and the display polypeptide are expressed as a fusion protein which is which is displayed on the surface of the replicable genetic package;

(6) recovering replicable genetic packages that are present in the selected tissue of the test animal at a suitable time after administration; and

(7) repeating (4) through (6), as necessary, to obtain a further optimized recombinant delivery vehicle that exhibits further enhanced ability to enter a selected mammalian tissue upon administration to a mammal.

39. The method of claim 37, wherein the replicable genetic package is a bacteriophage.

40. The method of claim 39, wherein the bacteriophage is M13.

41. The method of claim 40, wherein the polynucleotide which encodes a display polypeptide is selected from the group consisting of gene III and gene VIII.

42. The method of claim 37, wherein the selected mammalian tissue is the bloodstream and the administration is by inhalation.

43. The method of claim 37, wherein the administration is intravenous and the selected mammalian tissue is selected from the group consisting of lymph node and spleen.

44. A method for evolving a vaccine delivery vehicle to obtain an optimized delivery vehicle having enhanced specificity for antigen-presenting cells, the method comprising:

(1) recombining members of a pool of polynucleotides to produce a library of recombinant polynucleotides;

(2) producing a library of replicable genetic packages, each of which comprises a member of the library of recombinant polynucleotides operably linked to a polynucleotide that encodes a display polypeptide, wherein the recombinant polynucleotide and the display polypeptide are expressed as a fusion protein which is which is displayed on the surface of the replicable genetic package;

(3) contacting the library of recombinant replicable genetic packages with a non-APC to remove replicable genetic packages that display non-APC-specific fusion polypeptides; and

(4) contacting the recombinant replicable genetic packages that did not bind to the non-APC with an APC and recovering those that bind to the APC, wherein the recovered replicable genetic packages are capable of specifically binding to APCs.

45. The method of claim 44, wherein the method further comprises the steps of:

(5) recombining a nucleic acid which comprises at least one recombinant polynucleotide obtained from a replicable genetic package that is capable of specifically binding to APCs with a further pool of polynucleotides to produce a further library of recombinant polynucleotides;

(6) producing a further library of recombinant replicable genetic packages, each of which comprises a member of the library of recombinant polynucleotides operably linked to a polynucleotide that encodes a display polypeptide, wherein the recombinant polynucleotide and the display polypeptide are expressed as a fusion protein which is which is displayed on the surface of the replicable genetic package;

(7) contacting the further library of recombinant replicable genetic packages with a non-APC to remove those that display non-APC-specific fusion polypeptides; and

(8) contacting the recombinant replicable genetic packages which did not bind to the non-APC with an APC and recovering replicable genetic packages which bind to the APC, wherein the recovered replicable genetic packages are capable of specifically binding to APCs; and

(9) repeating (5) through (8), as necessary, to obtain a further optimized recombinant delivery vehicle which exhibits further enhanced specificity for antigen-presenting cells.

46. A method for evolving a vaccine delivery vehicle to obtain an optimized delivery vehicle having enhanced ability to enter a target cell, the method comprising:

(1) recombining at least first and second forms of a nucleic acid which encodes an invasin polypeptide, wherein the first and second forms differ from each other in two or more nucleotides, to produce a library of recombinant invasin nucleic acids;

(2) producing a library of recombinant bacteriophage, each of which displays on the bacteriophage surface a fusion polypeptide encoded by a chimeric gene that comprises a recombinant invasin nucleic acid operably linked to a polynucleotide that encodes a display polypeptide;

(3) contacting the library of recombinant bacteriophage with a population of target cells;

(4) removing unbound phage and phage which is bound to the surface of the target cells; and

(5) recovering phage which are present within the target cells, wherein the recovered phage are enriched for phage that have enhanced ability to enter the target cells.

47. The method of claim 46, wherein the method further comprises:

(6) recombining a nucleic acid which comprises at least one recombinant invasin nucleic acid obtained from a bacteriophage which is recovered from a target cell with a further pool of polynucleotides to produce a further library of recombinant invasin polynucleotides;

(7) producing a further library of recombinant bacteriophage, each of which displays on the bacteriophage surface a fusion polypeptide encoded by a chimeric gene that comprises a recombinant invasin nucleic acid operably linked to a polynucleotide that encodes a display polypeptide;

(8) contacting the library of recombinant bacteriophage with a population of target cells;

(9) removing unbound phage and phage which is bound to the surface of the target cells; and

(10) recovering phage which are present within the target cells; and

(11) repeating (6) through (10), as necessary, to obtain a further optimized recombinant delivery vehicle which exhibits further have enhanced ability to enter the target cells.

48. The method of claim 47, wherein the method further comprises:

(12) inserting into the optimized recombinant delivery vehicle a polynucleotide which encodes an antigen of interest, wherein the antigen of interest is expressed as a fusion polypeptide which comprises a second display polypeptide;

(13) administering the delivery vehicle to a test animal; and

(14) determining whether the delivery vehicle is capable of inducing a CTL response in the test animal.

49. The method of claim 47, wherein the method further comprises:

(12) inserting into the optimized recombinant delivery vehicle a polynucleotide which encodes an antigen of interest, wherein the antigen of interest is expressed as a fusion polypeptide which comprises a second display polypeptide;

(13) administering the delivery vehicle to a test animal; and

(14) determining whether the delivery vehicle is capable of inducing neutralizing antibodies against a pathogen which comprises the antigen of interest.

50. The method of claim 46, wherein the target cell is an APC.

add 47

add B1

add B7